REMARKS/ARGUMENTS

Claims 13-16, 20-24, 27-32, 36-44, and 48-52 are pending in the present application. The claims remain rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bergquist *et al.* (WO 95/14770). According to the Office Action, this reference discloses a *Thermus filiformis* DNA polymerase allegedly having reverse transcriptase activity in the presence of magnesium and comprising the modified motif recited in the claims (*i.e.*, the amino acid at position 4 is mutated to an amino acid other than E, A, G, or P). In particular, the Examiner refers to the subsequence LSDRIHLLHPE, which meets some of the requirements of the modified motif of the invention, in that position 4 of the subsequence is not E, A, G, or P. This subsequence occurs at residue 146 of the *T. fifliformis* enzyme.

Applicants note with appreciation the time taken by the Examiner in the telephone interview on March 10, 2006 to discuss this rejection. As noted previously and during the interview, the native from of the claimed DNA polymerases, unlike those of Bergquist, comprise ***a polymerase domain*** comprising the recited motif. During the interview, the Examiner acknowledged that clarification of the location of the polymerase domain and evidence that the subsequence noted above is outside this domain could overcome this rejection.

Based on that conversation, applicants now provide evidence clarifying the location of the polymerase domain in DNA polymerases from *T. filiformis* and other organisms. Moreover, as explained below, the subsequence cited by the Examiner is clearly outside this region.

The presence of conserved functional domains in DNA polymerases was well known at the time of the invention and is discussed in the specification on page 13, lines 9-17. As noted previously, it was well known in the art that such domains could be identified in a particular enzyme by sequence alignment with previously characterized enzymes. On page 13, line 12, applicants cite (and incorporate by reference) Blanco *et al.*, *Gene* (1991)100:27-38 (attached as Exhibit 1) which describes the general structure of DNA polymerases. Figure 3 of that reference delineates the polymerase and exonuclease domains of Pol I of *Escherichia coli* and states that the polymerase domain is located in the C-terminal portion (residues 521 to 928)

of the polymerase. Figure 2 of this paper provides a sequence alignment of "the highly conserved C-terminal regions" of various DNA polymerases, including the *T. aquaticus* polymerase (noted as Taq in Figure 2). There it can be seen that the C-terminal polymerase domain of *T. aquaticus* polymerase extends from about residue 484 to the C-terminus.

Furthermore, at the time of the invention, the structure of the *T. aquaticus* polymerase had been solved by Kim et al., *Nature* (1995) 376:612-616 (Exhibit 2). Kim's structure resolves the various domains of this polymerase and defines the polymerase domain to encompass residues 424-831 (see last nine lines in caption to Figure 2).

Thus, Blanco *et al.* establishes that DNA polymerases from a variety of organisms comprise a highly conserved polymerase domain in the C-terminal portion of the enzyme. Consistent with Blanco *et al.*, Kim *et al.* establishes the precise location of the polymerase domain in *T. aquaticus*. Using standard sequence alignment methods one of skill could easily identify the same domain in other enzymes.

Indeed, Bergquist *et al.* provide such a sequence alignment in Figure 2 of the application. In particular, Figure 2 shows an alignment of *Thermus spp.* polymerase sequences by which the C-terminal polymerase domain of *T filiformis* can be determined. As can be seen there, the C-terminal polymerase domain of *T. aquaticus* (residues 424-831) aligns with high identity to the C-terminal portion of the *T. filiformis* polymerase sequence.

The identity of the C-terminal polymerase domain of the *T. filiformis* polymerase is further clarified by Jung *et al.*, *Mol. Cells* (1997) 7:769-776 (Exhibit 3), which describes the cloning and analysis of the gene encoding the *T. filiformis* polymerase. Jung *et al.* provide an alignment of Pol I (abbreviated Eco), Taq polymerase and the *T. filiformis* polymerase in Figure 4 (page 773). There it can be seen that Pol I C-terminal polymerase domain (521-928) corresponds to residues 424-831 of DNA polymerases from both *T. aquaticus* and *T. filiformis*.

All of the evidence discussed above is reinforced by Table 1 on page 12 of the present application, which shows the location of the claimed motif in a number of enzymes of the invention. Table 1 makes clear that the correct motif in the *T. filiformis* enzyme is located on

the C-terminal portion of the protein (at position 679) and aligns with similar motifs in the C-terminal polymerase domains of other DNA polymerases, including that from *T. aquaticus*.

Based on all of the above, it is clear that the polymerase domain of a given DNA polymerase, including that from *T. filiformis*, could easily be identified by one of skill at the time of the invention using well known techniques. The evidence discussed above establishes that the polymerase domain of this enzyme is on the C-terminal portion of the enzyme and extends from about residue 424 to about residue 831. The claimed methods require an enzyme which, in its native form, comprises a polymerase domain comprising the claimed motif. Since the subsequence of the Bergquist relied on by the Examiner is clearly outside the polymerase domain (*i.e.*, at position 146), the enzyme disclosed there does not meet the requirements of the enzymes used in the claimed methods.

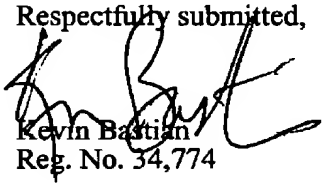
Since the Bergquist *et al.* patent application fails to disclose a DNA polymerase with the claimed motif in the polymerase domain, it fails to meet all the limitations of the pending claims. Applicants respectfully request that the rejection be withdrawn.

Finally, Applicants note that the Examiner continues to dismiss evidence that Bergquist *et al.* did not actually demonstrate reverse transcription using their enzyme. Although these arguments are note reiterated here, Applicants continue to take the position that the evidence provided in that application is not sufficient to establish the activities allegedly shown there.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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